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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/876,187	06/05/2001	Stuart A. Lipton	P-LJ 4714	5845

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/876,187	LIPTON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed March 29, 2004 (hereinafter referred to as "the response") has been entered. Claims 21-57 have been cancelled.

Accordingly, Claims 1-20 remain pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of differentiating progenitor cells, particularly embryonic stem cells and hematopoietic stem cells. The claims encompass *in vivo* and *in vitro* applications of the method.

Even as late as 2001, the art acknowledged that gene transfer into human hematopoietic stem cells was problematic (Hanazono et al., 2001). The claimed invention must be enabled at the time of filing. However, the priority date of this application is June 5, 2000. Thus, the instant specification must provide an enabling disclosure for the claimed invention as of this priority date.

The specification fails to provide an enabling disclosure for the genetic modification of human ES cells. The recent literature addresses the difficulties encountered in attempting to transfect human ES cells. Zwaka et al. (2003) points out that there are significant differences between mouse and human ES

cells and that "[h]igh, stable transfection efficiencies in human ES cells have been difficult to achieve, and, in particular, electroporation protocols established for mouse ES cells work poorly in human ES cells" (abstract). Thus, it is clear that the behavior of mouse ES cells is not predictive of human ES cells. In April 2001, Eiges et al. compared the efficiency of several different transfection protocols for human ES cells. The reference demonstrates use of the transfection protocol of ExGen 500 to transfect human ES cells. However, the instant specification teaches the use of adenovirus transduction for the genetic modification of human ES cells. Example 6 of the specification describes the transfection of human ES cells with an adenovirus carrying the β-galactosidase reporter gene. Although the disclosure states that "[s]taining for expression of the β-galactosidase marker gene was performed," no results are provided with regard to the detection of β-galactosidase-expressing cells. Thus, at the time of filing, methods for successfully transfecting human ES cells were not known. The teachings of Eiges et al. (2001) would not have been available to the skilled artisan as of the filing date of this application which is July 27, 2000.

Regarding gene transfer into human HSCs, even as late as 2001, the art acknowledged that gene transfer into human hematopoietic stem cells was problematic (Hanazono et al., 2001). The claimed invention must be enabled at the time of filing. However, the priority date of this application is June 5, 2000. Thus, the instant specification must provide an enabling disclosure for the claimed invention as of this priority date.

The specification contemplates that transfecting the ES cells with a nucleic acid encoding an MEF2 and contacting the cells with a differentiating agent will be sufficient to direct the cells to differentiate *in vivo* or *in vitro* into the appropriate cell type and functionally integrate into the tissue into which they are implanted. However, the state of the art for *in vivo* differentiation of ES cells is undeveloped. While much work has been done to develop techniques for the directed differentiation of ES cells *in vitro* to produce desired cell types, little is known about the behavior of these cells *in vivo* or

how they will interact with the local environment when implanted into adult tissues. Jackowski (1995) details the limitations and unpredictability associated with the transplantation of neural tissue.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of stem or progenitor cell types that could be used, and the unpredictability for producing cells suitable for therapeutic transplantation, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention to produce useful cell compositions.

At page 6, paragraph 1 of the response, Applicants argue that electroporation can be useful for transfecting human progenitor cells because Figure 1 of Eiges et al. shows luciferase reporter gene activity when human ES cells were transfected by electroporation. Although very low levels of reporter gene activity were detected in cells transfected by electroporation, the reference also states that "human ES cells do not survive electroporation well" (p. 515, column 1, paragraph 1). Furthermore, the instant specification does not teach transfecting human ES cells by electroporation, but rather teaches using adenovirus transduction for the genetic modification of ES cells (see Example 6). No results are provided for the adenovirus transduction experiments.

At page 7, paragraph 1 of the response, Applicants argue that the claimed methods of differentiating progenitor cells do not require high efficiency transfection, because "one skilled in the art understands that cell populations **stably expressing** an introduced nucleic acid molecule can be routinely prepared using, for example, standard methods such as antibiotic selection in order to select for a transfected population of cells" (emphasis added). However, there is no evidence that the transduction method disclosed in the specification, i.e. adenovirus transduction, can be used successfully to obtain cells that stably express the introduced nucleic acid. Furthermore, since the specification does not disclose what level of transfection efficiency is needed to carry out the claimed method for producing a useful cell composition, suitable for therapeutic transplantation, it is not evident that high efficiency transfection is

not needed. Likewise, it is not evident that the transfection methods disclosed in the specification would provide even a low level of transfection. The specification does not show that low level transfection would be suitable for the differentiation protocol recited in the claims, nor does it show that cell compositions resulting from low level transfection would have the use asserted in the specification, which is for therapeutic transplantation. Applicants further asser that the specification discloses the selection of MEF2c-expressing P19 ES cells using a neomycin resistance gene and selection with geneticin. However, P19 cells are a mouse cell line and therefore could not be used for therapeutic transplantation, which is the only patentable utility asserted in the specification for the cell compositions produced by the claimed methods, nor are they subject to the transfection difficulties being argued here, which is exclusively a problem relating to the transfection of **human** stem cells.

At page 8, paragraph 1 of the response, Applicants argue that when the genetically modified cells recited in the claims are transplanted prior to differentiation, "the neuronal environment can drive the cells into the desired neuronal cell type **due to the presence of appropriate environmental cues**" (emphasis added). While this may be the case in healthy animals, it is not true in diseased animals. Applicants are reminded that there is no patentable utility for transplanting cells into healthy animals; rather the cell compositions produced are intended for transplantation to diseased animals having an ongoing pathological process. Such environments do not provide the "appropriate environmental cues" that Applicants refer to. Furthermore, Jackowski points out that extracellular matrix-associated molecules that **inhibit** the successful regeneration of adult mammalian CNS axons are present within the CNS.

At page 8, paragraph 1 of the response, Applicants point to Liu et al. (2000) as evidence that *in vivo* differentiation of progenitor cells will work. However, Liu et al. describes the use of healthy rats that have an induced lesion. Such animals do not have the disadvantage of exhibiting an ongoing pathological process. Applicants further cite Deacon et al. (1998). Once again, the experiments described were carried out in healthy animals, not diseased animals.

At page 9, paragraph 2 of the response, Applicants dismiss the reference of Jackowski et al. (1995) as not representative of the state of the art in the year 2000.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Dianiece Jacobs, whose telephone number is (571) 272-0532.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER